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Pharmacology in Space Medicine

by

V. E. Belay et al

UNITED STATES AIR FORCE
SCHOOL of AEROSPACE MEDICINE

AEROSPACE MEDICAL DIVISION (AFSC)
BROOKS AIR FORCE BASE, TEXAS

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V. E. Belay et al

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Future, long, manned flights on orbiting space stations as well as on lunar and interplanetary spacecraft present a number of new pharmacological problems. The different aspects of this task, such as effective drugs for crewmembers, prognosis of possible changes in their condition, evaluation of physiologic variables, possible acute or chronic illnesses (and treatment of same on the spacecraft) must be carefully studied and adequately resolved based on the specific missions to be accomplished. Moreover, spacecraft structure [and size], number and role of crewmembers must also be considered.

Rational utilization of medications will be one of the cardinal aspects in programming future space missions. At present, we contemplate the use of medications to:

1. stimulate natural compensatory and adaptation mechanisms to increase tolerance to extreme flight factors,

2. treat an illness,

3. enhance performance, eliminate fatigue and emotional stress.

For this purpose, besides dipping into the arsenal of available drugs, new compounds with a specific effect will also have to be developed. At this particular point and time, it is imperative to find the most practical administration methods based on space flight conditions and expiration date of the preparations. Probably, the best form will be tablets and disposable injection syringes.

Amount and type of on-board medical supplies and equipment will be dictated by the duration and nature of the mission, the presence of a physician in the spacecraft, the size of the spacecraft, its payload and a series of other specifications.

As we know, a small amount of medications was carried in all Soviet and American space missions. They included analeptics, analgesics, antiradiation drugs, etc. (59). As programmed, Cooper injected himself

with dexedrine during the last orbit, although his mental and physiologic condition did not require it (53). As indicated by Dr. Berry such a medication can, to a certain degree, mitigate possible fatigue and increase psychomotory performance. We believe that great emphasis should be placed on the possibility of using stimulants during long space missions as well as for different critical situations.

Undoubtedly, during long space missions, direct indications for drugs may be necessary, requiring a careful prognosis, and consequently a well-thought out approach in the selection of the on-board medical supplies. Along with the possible indications for drugs, one must also study the characteristic physiologic responses to individual space flight factors as well as their complex effect, because..."one and the same medication, taken...under different physiologic conditions, can be remedial or poisonous". We believe that this is substantiated by our data on different responses to medications following acceleration (36).

Consequently, the study of the specific effect of medications under laboratory experimental conditions (G loads, weightlessness, prolonged isolation, etc.) and possible emergency situations (change in environmental gases, radiation effects, upset in meal schedule, etc.) is ~~not only important,~~ but a necessary stage in the preparation for long space missions. Griffenhagen (62) has expressed similar opinions on this subject.

Two basic aspects of the general problems of space pharmacology are:

1. enhance body tolerance to extreme flight factors and

2. natural response to medications during the simulation of some space-flight stresses.

Among the methods considered to improve body tolerance to extreme flight stresses, medications represent an important aspect. At present, we have sufficient facts supporting the possibility and propriety of the use of medications for this purpose. Moreover, in past missions some aspects of the problems in question were put into practice. G forces, weightlessness, radiation and hypoxia should be considered as cardinal stresses in trying to increase body tolerance by means of medications. The requirement for different approaches to increase tolerance to G

forces (among them also medications) is stipulated, first of all, by the possible occurrence of situations where the degree and duration of the acceleration effect can reach the limits of physiologic endurance. This can bring about not only an important decrease in the performance of the pilot, but also harmful consequences.

The merit of different drugs capable of enhancing body tolerance to acceleration was evaluated by investigators in our country as well as abroad (2,10,11,25,31,41,42,55,56,63,68). However, to date, this research work has been limited to animal experimentation and the results are quite controversial, even for one and the same preparation.

The medications used by the authors of this paper are shown in Table 1. Our experimental work has evidenced that because of the functional changes brought about by the medications it is possible to increase or improve considerably the tolerance to transverse acceleration. Based on their effect, here is a list of drugs which showed positive results: narcotics and analeptics, central stimulants and sedative agents, cardiovascular agents, etc. The degree of effect depends on the type of preparation, the dose, administration (per os, injection, etc.) nd frequency of administration. Best results were obtained with st. chnine, some sympathomimetic agents (phenamine, adrenalin, noradrenalin) and narcotics. Administration of the aforementioned drugs at optimal doses decreased animal mortality and cardiovascular deconditioning caused by G forces (Fig. 1), (8,13).

Many other authors obtained the same positive results by using different drugs to increase tolerance to G forces (9,24,41,42,67 et al).

We possess, therefore, basic indications that the administration of different agents represents one of the prospective and important means to increase body tolerance to G forces. We are now faced with the problem of selecting the most effective medications as well as the optimal form of their administration under space flight conditions. In trying to reach a decision, two basic factors must be considered: (a) phases and conditions of flight; and (b) the properties of the medications. During the first phase of flight (lift-off) there will hardly be a need for a special medication because preflight training fully conditions the cosmonaut to satisfactorily tolerate G loads. However, during re-entry an indication for medications may exist. First of all, one must consider that after hypodynamia [gravity-free state, inactivity] tolerance to acceleration stresses decreases (32, 50); this is expected to be even more so after long missions. Under

these conditions, we may be justified to administer appropriate medications only as a preventive measure.

We must also keep in mind the possibility of an emergency situation causing a sudden increase in the gradient of G forces to critical levels, which would require quick correction and use of drugs.

Based on available data and on the effect of different agents on the tolerance to G forces and based on their pharmaceutical properties, we must assume that the best suited preparations for the purpose in mind will be some of the sympathomimetic and central stimulant agents such as phenamine, strychnine, Securinin, etc. These drugs not only increase tolerance to G forces, but possess also many other properties that are very helpful under space flight conditions (3,27). We are skeptical about the usefulness of narcotics and tranquilizers under these conditions since they decrease tolerance to stress factors (13,64), and some of their properties are undesirable for the specific effects of space flight. The use of tranquilizers should be limited to correct functional aberrations (69); they may be taken only in cases of dire necessity, however, never before re-entry.

Available data attest to the possible occurrence of different, important functional changes under weightless conditions (16,17,30,47, 48,49,59,61,65,66, et al). The nature and symptomatology of these disorders may vary depending on the factors involved—nature and duration of mission, training of cosmonauts to the specific effects of weightlessness, reaction of the vestibular apparatus, etc. In some instances, cardiovascular disorders due to prolonged hypodynamia, decreased afferent stimulation, and autonomic disorders complicated by motion sickness symptomatology may prevail. The use of drugs, however, is fully justified for prophylactic reasons and for treating the aforementioned disorders. The selection of the medications must be based on the nature of the disorders. In fact, in the case of decreased cardiovascular system tonus and orthostatic disorders, some analeptics are indicated (phenamine, caffein, etc.) as well as stimulants (strychnine, Securinin, ginseng and eleuterococcus extracts*, and others). Administration of cholinolytic agents (metamizil, pentaphen and others) is helpful in correcting the motion sickness syndrome.

*Trans. Note: Those interested in experimental work carried out with these extracts may find it interesting to read The Effect of an Extract of Ginseng on the Adrenal Cortex and Eleutherococcus Senticosus-A New Medicinal Herb of the Araliaceae Family. Both papers are in the book on Pharmacology of Oriental Plants, Proceedings of the Second International Pharmacological Meeting, August 20-23, 1963 available at the USAFSAM Aeromedical Library, Brooks AFB, Texas.

Special compounds, however, aimed at correcting the pathogenesis of motion sickness (choline and adrenalin agents, central stimulants, antihistamines and others) would be much more effective.

Although, based on the present radiobiologic knowledge on antiradiation drugs (ionizing radiation) a fair amount of protection can be offered, yet not all necessary measures can be fully employed under space flight conditions. This is mainly due to the complex spectrum of cosmic radiation, the biologic effect of which is not, as yet, fully understood. However, under these conditions the body is exposed to the effect of combined and successive factors which will stipulate the complexity of the physiopathologic syndrome of the disorders occurring during space flight. Consequently, the problem of finding antiradiation drugs applicable to the specific conditions of space flight requires a special solution.

Presently, several drugs are successfully used by clinicians in radiation therapy (cysteamine, cystamine, AET, serotonin, etc.). Some of these (cysteamine, cystamine) could be included in the medicine chest as a prophylactic measure against radiation illness. However, we must keep in mind that certain, effective antiradiation drugs decrease body tolerance to the effect of other flight factors, and in part also to G forces and vibration (43). The aforementioned agents should, therefore, be used together with other drugs which can decrease the unfavorable response to antiradiation drugs.

Oxygen deficiency during a space mission could present a problem only in the case of an emergency. Under these conditions medications would be mandatory. Available literature supports the expediency and prospective use of drugs to increase body tolerance to oxygen deficiency (1,14,18,19,29,39,40, et al). Compounds decreasing tissue oxygen requirement (tranquilizers, narcotics, antioxydation agents) as well as stimulants of the central nervous sytem, the cardiovascular system, etc. would be best suited for this purpose. Hibernation should also be considered (5,23, et al). The pragmatical usefulness of drugs to increase tolerance to oxygen deficiency under different space flight conditions also remains to be determined.

Such being the case, the medicine chest should be supplied with drugs capable of increasing tolerance to all space flight factors. Moreover, one must also consider the possible occurrence of a frankly pathologic state. For this purpose, the medicine chest should also contain large spectrum antibiotics, antipiretics, analgesics, disin-

fectants, etc. The choice of the medications and their form of administration will be determined by the nature and tasks of the mission.

As mentioned earlier, the importance of pharmacology grows with the broadening of space exploration. In this connection, basic consideration must be given to the purpose and propriety of different prophylactic and curative agents and to the possibility of enhancing the cosmonaut's physical and mental capabilities during flight (53, 60,69).

In our opinion, too little emphasis has been placed on the specificity of the different pharmacological preparations administered so far and on their effect on physiological variances. Research carried out in the last few years in different countries, mainly in the Soviet Union and the USA, has contributed important theoretical and practical data on the physiological changes in the organism of man and animals exposed to G loads, vibrations, ionizing radiation, prolonged hypodynamia, etc. They indicate that depending on the actual situation in flight and on the time at which a certain drug may be indicated, the physiologic response to the administered medications may change when important functional changes are present. Pharmacologists are well acquainted with the basic physiologic reaction to different agents. Experience has shown, in a large number of cases, that when the body is exposed to unusual factors, its sensitivity to pharmaceutical substances may change considerably; in some cases this has led to pathologic responses. In fact, therapeutic dosages of cardiac glycosides may be toxic after prolonged hypoxic hypoxia (36) or following prolonged exposure to transverse G forces (38), etc. In this connection, it is evident that in space medicine great emphasis must be placed on responses to drugs. In fact, this is imperative, since we are concerned with man being exposed to a series of unusual stresses, for which defense and adaptation mechanisms to their effect have not been learned as yet. This is confirmed by available data on the influence of such factors as radiation, G forces and changes in ambient air. We must also take into account that many important facets of space medicine have been only slightly investigated. First and paramount are the problems of the physiologic effect of prolonged weightlessness. Which are the space-flight stresses we must consider to uncover idiosyncrasies? Apparently all new situations man may encounter under these unusual circumstances, such as:

1) dynamic factors (G forces at lift-off and re-entry, angular acceleration, vibration, weightlessness),

2) factors conditioned by the construction of the spacecraft (changes in environmental parameters, restricted mobility, peculiarities of solid and fluid diet, etc.),

3) space factors (different ionizing radiation from the Van Allen belt, solar flares, etc.),

4) factors peculiar to the vital activity of the astronauts (stresses on the nervous system and mental functions related to monotonous tasks, changed day-night cycle, prolonged confinement, uniform surroundings, greatly decreased afferent stimulation, etc.).

The complex action of the aforementioned factors can, of course, bring about different important physiologic changes and consequently alter the response to medications during a long space mission. We have found varied responses to different drugs after exposure to transverse G forces and to different gas mixtures. However, we have observed that individual responses vary and depend upon certain conditions. Some of these are:

1. intensity and duration of stress factors,

2. prevalent influence on any one physiologic function,

3. specific and constitutional peculiarities as well as sex and age,

4. pharmacodynamic properties of the medications.

Our experimental work, carried out on animals, has revealed a relationship between degree of response to medications and that of physiological changes following exposure to transverse acceleration. In fact, we have observed a sudden increase in the sensitivity to cardiac glycosides (strophanthin-K, Convagid), to narcotics (short acting barbiturates, ether, chloral hydrates, etc.) as well as to other agents following the exposure to prolonged G forces (up to 2 hrs) which cause important changes in the cardiac function. Moreover, similar stresses decrease the sensitivity of the organism to some analeptic drugs (caffeine, Corasol, Zititon, etc.). Sensitivity to adrenalin also evidenced great variations. Based on the intensity of the G forces and on the individual response to centrifugation, we found increased, decreased or perverse reactions to adrenalin following exposure (Fig. 2). We believe that these data are extremely important because they offer a better insight into the mechanism of the physio-

logic disorders as well as better indications for the administration of an appropriate medication whenever this becomes necessary.

Analogous data are available for different gas mixtures. In fact, research work performed by Dmitrieva (26) and other authors has shown conclusive proof that hypoxia greatly increases sensitivity to cardiac glycosides. Short or prolonged hypoxia alters physiologic responses to radiation effects (5,6) and the duration of some infections (44). Data are also available on increased sensitivity to some agents in the presence of hyperoxia (45, et al). A change in oxygen partial pressure also brings about varied physiologic responses to many factors as well as some medicamentations.

Our findings have shown that different CO_2 concentrations are equally responsible for important changes in body sensitivity to pharmacological agents. Here again, manifestations and degree of changes are stipulated by the aforementioned conditions (duration and intensity of stress factors, properties of pharmacological agents, etc.) (Fig. 3). Data on the influence on physiologic reactions due to the combined effect of hypercapnia and hypoxia are of special interest. In fact, some of our experimental projects were aimed at gaining better knowledge in this area.

Present spacecraft as well as prospected EVA do not exclude the effect of prolonged angular accelerations and other factors leading to the motion sickness syndrome. Prophylaxis and treatment of motion sickness have been the object of much research work, however, too little emphasis has been placed on possible changes in physiologic responses under these conditions. Based on experimental work carried out by Pustov (37,38), motion changes, first of all, the functional tonus of the emetic center which, in turn, increases body sensitivity to apomorphine. Apparently, functional changes in the CNS are not limited to the emetic center, and the use of different drugs will afford a better insight of the specific physiologic responses to these conditions.

Our knowledge in this area is limited mainly because of the difficulties involved in simulating weightlessness under laboratory conditions. In recent years, different investigators have exposed subjects to prolonged bed rest or to immersion, and data available on physiologic responses to some medications under these conditions are only fragmentary (70). However, these studies were limited to the response of the autonomic nervous system, and neglected responses of the cardiovascular system to medications. The use of certain

pharmacological agents could preserve an adequate cardiac function and tonus of the peripheral vessels; future investigations will, by all means, throw a light also on this important facet of our quest.

Ionizing radiation, a thoroughly investigated factor of space flight, can bring about different functional disorders. In fact, important changes in the adaptation and regulatory mechanisms of the nervous and endocrine systems have been observed. They condition, first of all, the physiologic responses to different external environmental factors as well as to drugs (7,21,22 et al). Based on experimental data, it can be stated that physiologic responses to medications depend upon the severity of the symptoms and degree of possible radiation damage. For example, in the first hours after exposure to ionizing radiation the effect of barbituric acid is clearly weakened (20,28, et al); however, at the time of the severest manifestations of the disease sensitivity to barbiturates increases considerably. Moreover, conclusive data was also obtained with ether, nitrous acid derivatives and other narcotic substances (33,46, et al). Physiologic responses to cardiovascular agents in the presence of radiation illness are often altered. In fact, during the early stages or the incubation period, the vasoconstrictor action of adrenalin, pituitrin and other pharmacological agents is decreased, however, at the height of the illness it is enhanced (12,35,51,54, et al).

Valuable data is also available on the physiologic responses to analeptics, central and cardiovascular stimulants, chemotherapeutic agents, diuretics, and others.

The aforementioned data attest to the fact that ionizing radiation can change considerably the physiologic responses to many pharmaceutical agents. Consequently, to select the most rational methods of administration and to avoid possible complications, it is imperative to learn the peculiar action of the pharmacological agents during the different phases of the radiation disease.

Our experimental data, as well as those in literature, show, beyond a doubt, that even the isolated effect of individual space stress factors entails important changes in the physiologic response to pharmacological agen... These findings are of great practical importance for the problem at hand——space pharmacology. Unless we possess the knowledge of the peculiar action of drugs during simulation of different space-flight stresses the cosmonauts may not only be exposed to undesirable therapeutic effects but even to injurous

consequences. This is of extreme importance, mainly because during a space mission medical control of physiologic responses to drugs is quite difficult, and rendering qualified and specialized medical assistance may be impossible.

The influence of the space-stress factors complex on physiologic functions must be thoroughly investigated, especially response variances under these conditions. Data available on the combined influence of changes in temperature and G loads (58), hypoxia and G forces (34,57), ionizing radiation and G forces (4), as well as other combined factors give sufficient reasons for the urgency of widening the scope of the research work in this area with the aim of learning the peculiar physiologic responses under space equivalent conditions. As already recognized by several authors (9,36,52,69), the task of forging a new scientific discipline -"space pharmacology"- merits our highest concern.

In conclusion, we should concentrate our attention on:

1. the study of pharmacological agents that enhance physiologic tolerance to unfavorable space factors,

2. the study of the pharmacodynamic properties of different drugs based on various physiologic responses,

3. finding optimal dosages and administration methods for different drugs under simulated space flight conditions,

4. and on the use of pharmacological agents (as analysers* of physiologic functions) to understand the actual effects of space factors on the human body.

A successful solution of these highly important problems can be assured only by encouraging the cooperation of different specialists: pharmacologists, chemists (synthetic products), physiologists and clinicians.

*Trans. Note: literal translation.

Table 1*

Influence of pharmacological agents
on animal tolerance to transverse accelerations

Agents	Results
Narcotics (thiopental sodium, chloral hydrate, and others)	Small doses enhanced and large doses decreased tolerance.
Analeptics (caffeine, Corazol and others)	No consequential effect.
Phenamine, strychnine.	Enhanced tolerance at optimal doses.
Phenatin	Decreased tolerance.
Vascular stimulants (adrenalin, noradrenalin, ephedrine)	Enhanced tolerance.
Nitroglycerin, dibazol	No consequential effect.
Cardiac glycosides (strophantin-K)	Enhanced tolerance.
Antiradiation drugs (cysteamine, cystamine)	Decreased tolerance.

*Trans. Note: More detailed information on dosages and experimental procedures are given in a paper by the same authors: "Effect of some drugs on tolerance of accelerations", NASA Technical Translation, NASA TT F-226, p. 79 (available in Document Section, Aeromedical Library, Brooks AFB, Texas)

Figures

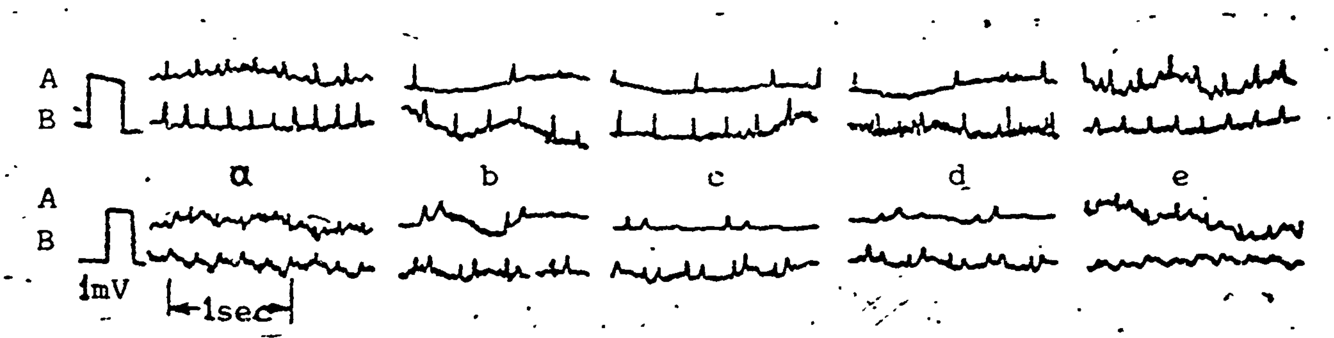

Fig. 1. ECG of rabbits exposed to transverse acceleration; control runs (A), after the administration of strychnine (B): a-before exposure; b,c,d-1st, 3rd and 6th minute of exposure; e-2 min. after exposure.

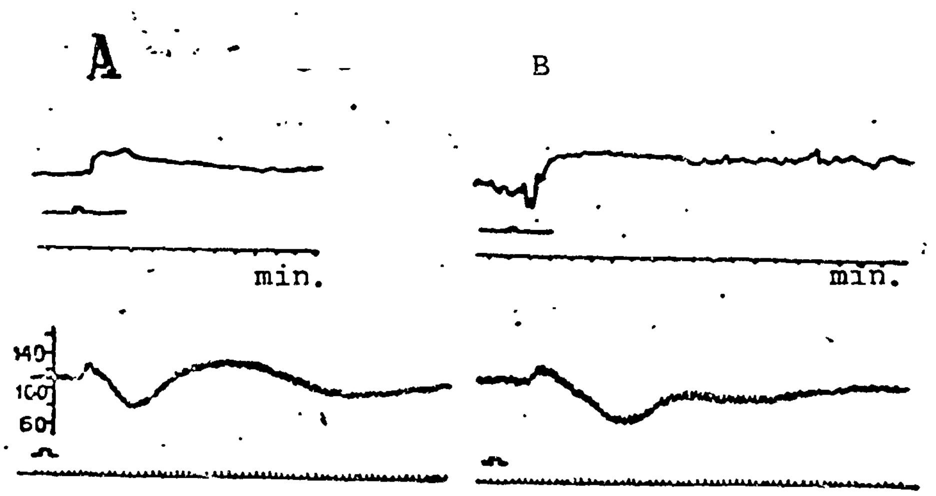

Fig. 2. Coronary circulation response (above) and blood pressure in the femoral artery (below) after the administration of 0.002 mg/Kg adrenalin before exposure (A) and 15 min. after (B) exposure to transverse acceleration of 12 Gs.

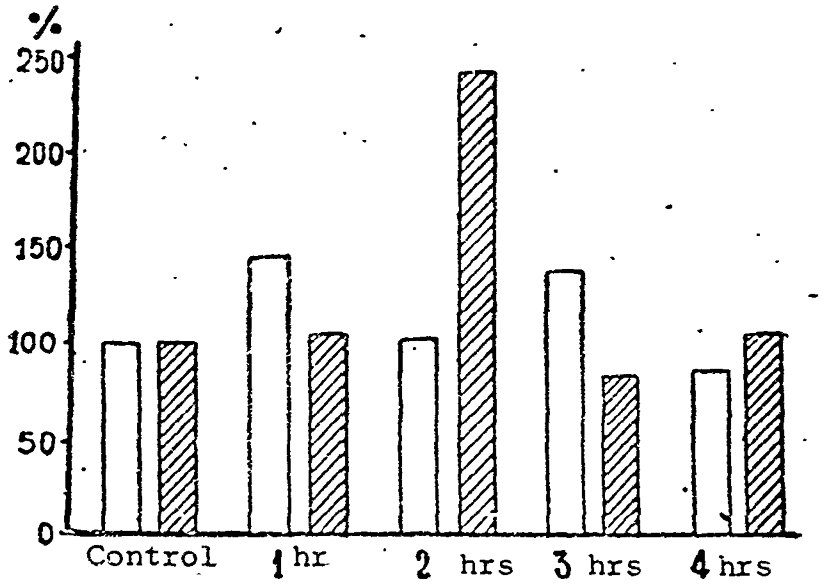

Fig. 3. Influence of CO_2 (8-10% in gas mixture) on the duration of ether (white columns) and of intraperitoneal* (dark columns) anesthesia in white mice. Ordinate: duration of anesthesia in percental values of control data; abscissa: exposure time to gas mixture.

*Trans. Note: In the Russian caption this term begins with the letters intra after which three letters are missing (not printed) and then narkonovogo. Since intra...narkonovogo or intranarkonovogo is not listed in any of the dictionaries available in our Section, the translator has liberally translated it as intraperitoneal.

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